DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 610

[Docket No. 1980N–0208]

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule and proposed order.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations in response to the report and recommendations of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel). The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, bacterial antitoxins, and immune globulins. On the basis of the Panel's findings and recommendations, FDA is proposing to classify these products as Category I (safe, effective, and not misbranded), Category II (unsafe, ineffective, or misbranded), or Category IIIB (off the market pending completion of studies permitting a determination of effectiveness). On December 13, 1985, FDA proposed to amend the biologics regulations and proposed to classify the bacterial vaccines and toxoids. After reviewing the Panel's report and comments on the proposal, FDA published a final rule and final order on January 5, 2004. The court vacated the January 5, 2004 (69 FR 255) final rule. Therefore, elsewhere in this issue of the **Federal Register**, FDA is withdrawing the January 5, 2004, final rule. FDA is issuing this proposed rule and proposed order again to provide notice and to give interested persons an opportunity to comment.

DATES: Submit written or electronic comments on the proposed rule and proposed order by March 29, 2005.

ADDRESSES: You may submit comments, identified by Docket No. 1980N–0208, by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. in the subject line of your e-mail message.
- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. for this proposal. All comments received will be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the process, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Astrid Szeto, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Introduction

In this document, FDA is issuing a proposed rule and proposed order to:

1. Categorize those bacterial vaccines and toxoids licensed before July 1972 according to the evidence of their safety and effectiveness, thereby determining whether they may remain licensed and on the market;
2. Issue a proposed response to recommendations made in the Panel's report.[1] These recommendations concern conditions relating to active components, labeling, tests required before release of product lots, product standards, or other conditions considered by the Panel to be necessary or appropriate for assuring the safety and effectiveness of the reviewed products;
3. Revise the standard for potency of Tetanus Immune Globulin in § 610.21 (21 CFR 610.21); and
4. Apply the labeling requirements in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57) to bacterial vaccines and toxoids by amending the implementation dates in § 201.59 (21 CFR 201.59).

[1] The Panel was convened on July 12, 1973, in an organizational meeting, followed by multiple working meetings until February 2, 1979. The Final Report of the Panel was completed in August 1979.

II. Background

A. History of the Review

In the **Federal Register** of February 13, 1973 (38 FR 4319), FDA issued procedures for the review by independent advisory review panels of the safety, effectiveness, and labeling of biological products licensed before July 1, 1972. This process was eventually codified in § 601.25 (21 CFR 601.25) (38 FR 32048 at 32052, November 20, 1973). Under the panel assignments published in the **Federal Register** of June 19, 1974 (39 FR 21176), FDA assigned the biological product review to one of the following groups: (1) Bacterial vaccines and bacterial antigens with "no U.S. standard of potency," (2) bacterial vaccines and toxoids with standards of potency, (3) viral vaccines and rickettsial vaccines, (4) allergenic extracts, (5) skin test antigens, and (6) blood and blood derivatives.

Under § 601.25, FDA assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the Commissioner of Food and Drugs which was to: (1) Evaluate the safety and effectiveness of the biological products for which a license had been issued, (2) review their labeling, and (3) identify the biological products that are safe, effective, and not misbranded. Each advisory panel report was also to include recommendations classifying the products reviewed into one of three categories.

- Category I designating those biological products determined by the panel to be safe, effective, and not misbranded.
- Category II designating those biological products determined by the panel to be unsafe, ineffective, or misbranded.
- Category III designating those biological products determined by the panel not to fall within either Category I or Category II on the basis of the panel's conclusion that the available data were insufficient to classify such biological products, and for which further testing was therefore required. Category III products were assigned to one of two subcategories. Category IIIA products were those that would be permitted to remain on the market pending the completion of further studies. Category IIIB products were those for which the panel recommended license revocation on the basis of the

panel's assessment of potential risks and benefits.

In its report, the panel could also include recommendations concerning any condition relating to active components, labeling, tests appropriate before release of products, product standards, or other conditions necessary or appropriate for a biological product's safety and effectiveness.

In accordance with § 601.25, after reviewing the conclusions and recommendations of the review panels, FDA would publish in the **Federal Register** a proposed order containing: (1) A statement designating the biological products reviewed into Categories I, II, IIIA, or IIIB, (2) a description of the testing necessary for Category IIIA biological products, and (3) the complete panel report. Under the proposed order, FDA would propose to revoke the licenses of those products designated into Category II and Category IIIB. After reviewing public comments, FDA would publish a final order on the matters covered in the proposed order.

In the **Federal Register** of November 21, 1980 (45 FR 77135), FDA issued a notice of availability of the Panel's final report. In the **Federal Register** of December 13, 1985 (50 FR 51002), FDA issued a proposed rule that contained the full Panel report[2] and FDA's response to the recommendations of the Panel (the December 1985 proposal) (Ref. 1). In the December 1985 proposal, FDA proposed regulatory categories (Category I, Category II, or Category IIIB as defined previously in this document) for each bacterial vaccine and toxoid reviewed by the Panel, and responded to other recommendations made by the Panel. The public was offered 90 days to submit comments in response to the December 1985 proposal.

The definition of Category IIIA as described previously in this document, was applied at the time of the Panel's review and served as the basis for the Panel's recommendations. In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA revised § 601.25 and codified § 601.26, which established procedures to reclassify those products in Category IIIA into either Category I or Category II based on available evidence of effectiveness. The Panel recommended that a number of biological products be placed into Category IIIA. FDA assigned the review of those products previously classified into Category IIIA to the Vaccines and Related Biological Products Advisory Committee. FDA has addressed the review and reclassification of bacterial vaccines and toxoids classified into Category IIIA through a separate administrative procedure (see the **Federal Register** of May 15, 2000 (65 FR 31003), and May 29, 2001 (66 FR 29148)). Therefore, FDA does not further identify or discuss in this document any bacterial vaccines and toxoids classified into Category IIIA.

B. Comments on the December 1985 Proposal

FDA received four letters of comments in response to the December 1985 proposal. One letter from a licensed manufacturer of bacterial vaccine and toxoid products concerned the confidentiality of information it had submitted for the Panel's review. As provided in § 601.25(b)(2), FDA considered the extent to which the information fell within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), before placing the information in the public docket for the December 1985 proposal. Another comment from a member of the Panel provided an update of important scientific information related to bacterial vaccines and toxoids that had accrued since the time of the Panel's review. The letter did not comment on the December 1985 proposal nor did it contend that the newly available information should result in modification of the Panel's recommendations or FDA's proposed actions. FDA's responses to the comments contained in the remaining two letters follow.

(Comment 1) One comment from a licensed manufacturer of bacterial vaccines and toxoids objected to the proposed classification into Category IIIA of several of its products for use in primary immunization.

As described previously in this document, FDA is considering those products proposed for Category IIIA in a separate rulemaking process.[3] This proposal does not propose any action regarding the further classification of those products proposed for Category IIIA, including those proposed for Category IIIA for primary immunization. All manufacturers and others in the general public have been offered additional opportunity to comment on the final categorization of specific Category IIIA products in the above-noted process.

(Comment 2) In response to FDA's proposal that Pertussis Immune Globulin (Human) be placed into Category IIIA because of insufficient evidence of efficacy, one comment stated that FDA should permit manufacture of Pertussis Immune Globulin (Human) for export only. The comment noted that medical practices in other countries may differ from those in the United States and that in some countries Pertussis Immune Globulin (Human) plays an important role in the augmentation of therapy with antibiotics in young, very ill infants with pertussis.

Since that time, FDA has revoked all licenses for Pertussis Immune Globulin (Human) at the requests of the individual manufacturers. The FDA Export Reform and Enhancement Act of 1996 (Public Law 104–134, as amended by Public Law 104–180) amended provisions of the Federal Food, Drug, and Cosmetic Act (the act) pertaining to the export of certain unapproved products. Section 802 of the act contains requirements for the export of products not approved in the United States. Under these provisions, products such as Pertussis Immune Globulin (Human) can be exported to other countries, if the requirements of section 802 are met.

(Comment 3) One comment concerned the generic order and wording for product labeling recommended by the Panel and which FDA proposed to adopt in its response to the Panel recommendation. The comment recommended that a labeling section concerning "Overdose" be included only when circumstances dictate. The comment stated that because all biological products are prescription products administered by health care providers, the risk of overdose should be greatly reduced.

FDA agrees that, in many cases, a labeling section in part 201 (21 CFR part 201) entitled "Overdosage" is not necessary. Section 201.56(d)(3) (21 CFR 201.56(d)(3)) of the labeling regulations provides that the labeling may omit any section or subsection of the labeling format (outlined in § 201.56) if clearly inapplicable. The "Overdosage" section, provided for in § 201.57(i) of the regulations, is omitted for many bacterial vaccine and toxoid products.

(Comment 4) One letter of comment objected to several statements made by the Panel and provided in the written report, but did not object to or comment on FDA's proposed responses to the Panel's recommendations.

FDA is not considering comments on the Panel's report in this proposed rule

[2] In addition to publication in the **Federal Register** of December 13, 1985 (50 FR 51002), FDA is making the full Panel report available on FDA's Website at *http://www.fda.gov/ohrms/dockets/default.htm*. A copy of the Panel report is also available at the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

[3] *See* the **Federal Register** of May 15, 2000 (65 FR 31003), containing the proposed order to reclassify Category IIIA products into Category I and Category II based on the review and recommendation of the Vaccines and Related Biological Products Advisory Committee.

and proposed order. The Panel's recommendations are not binding but represent the scientific opinions of a panel of experts. FDA believes that the agency should not modify the statements and recommendations of the Panel as provided in its report, including through public comment. The purpose of the opportunity for comment is to allow comment on FDA's responses to the Panel's report and not on the Panel's report directly.

In this proposal, FDA is again providing the opportunity for comment on FDA's proposals.

III. Proposed Categorization of Products—Proposed Order

Category I. Licensed biological products determined to be safe and effective and not misbranded. Table 1 of this document is a list of those products proposed in December 1985 by FDA for Category I. Under the "Comments" column, FDA notes those products for which FDA's proposed category differs from that recommended by the Panel. Products for which the licenses were revoked before the December 1985 proposal and that were already identified in the December 1985 proposal are not listed in the tables below. Products for which the licenses were revoked after the December 1985 proposal are identified in the "Comments" column. FDA proposes to adopt Category I as the final category for the following products.

TABLE 1.—CATEGORY I

Manufacturer/License No.	Products	Comments
Alpha Therapeutic Corp., License No. 744	Tetanus Immune Globulin (Human)	Although the Panel recommended that Tetanus Immune Globulin (Human), manufactured by Alpha Therapeutic Corp., be placed in Category IIIB, FDA proposed that it be placed in Category I[1]
Advance Biofactures Corp., License No. 383	Collagenase	
Armour Pharmaceutical Co., License No. 149	Tetanus Immune Globulin (Human)	Manufacturer's licensed name is now Centeon L. L. C. On July 26, 1999, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
Connaught Laboratories, Inc., License No. 711	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, and Diphtheria Antitoxin	On December 9, 1999, a name change to Aventis Pasteur, Inc. with an accompanying license number change to 1277 was granted to Connaught Laboratories, Inc. FDA revoked the licenses for these products at the request of the manufacturer on July 6, 2001, and August 2, 2001, respectively
Connaught Laboratories, Ltd., License No. 73	BCG Vaccine, Botulism Antitoxin (Types A, B, and E), Botulism Antitoxin (Type E), Tetanus Toxoid	On February 24, 2000, a name change to Aventis Pasteur, Ltd. with an accompanying license number change to 1280 was granted. On December 21, 2000, FDA revoked the license for Tetanus Toxoid at the request of the manufacturer
Cutter Laboratories, Inc., License No. 8	Plague Vaccine, Tetanus Immune Globulin (Human)	On October 5, 1994, the manufacturing facilities and process for Plague Vaccine were transferred to Greer Laboratories, Inc., License No. 308. On May 24, 1995, FDA revoked Cutter's license for Plague Vaccine at the request of Cutter, the previous manufacturer; the license for Greer Labs, Inc. remains in effect. Bayer Corporation now holds the license for Tetanus Immune Globulin (Human) under License No. 8
Eli Lilly & Co., License No. 56	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	On December 2, 1985, FDA revoked the license for Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed at the request of the manufacturer
Glaxo Laboratories, Ltd., License No. 337	BCG Vaccine	On July 17, 1990, FDA revoked the license for BCG Vaccine at the request of the manufacturer
Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238	Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed	On July 17, 1990, FDA revoked the license for Diphtheria Antitoxin at the request of the manufacturer. On July 27, 1993, FDA revoked the licenses for Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed at the request of the manufacturer
Lederle Laboratories, Division American Cyanamid Co., License No. 17	Cholera Vaccine, Tetanus Immune Globulin (Human)	On December 23, 1992, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer. On October 23, 1996, FDA revoked the license for Cholera Vaccine at the request of the manufacturer

TABLE 1.—CATEGORY I—Continued

Manufacturer/License No.	Products	Comments
Massachusetts Public Health Biologic Laboratories, License No. 64	Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Antitoxin, Tetanus Immune Globulin (Human), Tetanus Toxoid Adsorbed, Typhoid Vaccine	Although the Panel recommended that Tetanus Antitoxin be placed in Category IIIB, FDA proposed in the December 1985 proposal that it be placed in Category I. On October 26, 1988, FDA revoked the license for Typhoid Vaccine at the request of the manufacturer. On January 10, 1994, FDA revoked the license for Tetanus Antitoxin at the request of the manufacturer. On December 22, 1998, FDA revoked the license for Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed at the request of the manufacturer. On August 3, 2000, FDA revoked the license for Diphtheria and Tetanus Toxoids Adsorbed at the request of the manufacturer
Merck Sharp & Dohme, Division of Merck & Co., Inc, License No. 2	Tetanus Immune Globulin (Human)	The manufacturer is now known as Merck & Co., Inc. On January 31, 1986, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
Michigan Department of Public Health, License No. 99	Anthrax Vaccine Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Typhoid Vaccine	On November 11, 1998, a name change to BioPort Corporation (BioPort) with an accompanying license number change to 1260 was granted. The license for Typhoid Vaccine was revoked on June 25, 1985, at the request of the manufacturer. The license for Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed was revoked at the request of the manufacturer (BioPort) on November 20, 2000. The license for Pertussis Vaccine Adsorbed was revoked at the request of the manufacturer (BioPort) on April 22, 2003
Parke-Davis, Division of Warner-Lambert Co., License No. 1	Tetanus Immune Globulin (Human)	On November 19, 1983, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
Swiss Serum and Vaccine Institute Berne, License No. 21	Tetanus Antitoxin	Although the Panel recommended that Tetanus Antitoxin be placed in Category IIIB, FDA proposes that it be placed in Category I. On March 13, 1980, FDA revoked the license for Tetanus Antitoxin at the request of the manufacturer
Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140	Tetanus Immune Globulin (Human)	The manufacturer is now known as Baxter Healthcare Corporation. On July 27, 1995, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
University of Illinois, License No. 188	BCG Vaccine	On May 29, 1987, FDA revoked the license for BCG Vaccine at the request of the manufacturer
Wyeth Laboratories, Inc, License No. 3	Cholera Vaccine, Tetanus Immune Globulin (Human), Typhoid Vaccine (acetone inactivated), Typhoid Vaccine (heat-phenol inactivated)	On December 23, 1992, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer. On September 11, 2001, FDA revoked the licenses for Cholera Vaccine and Typhoid Vaccine (both forms) at the request of the manufacturer

[1] The Panel recommended that Tetanus Immune Globulin (Human) manufactured by Alpha Therapeutic Corporation be placed in Category IIIB, products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce. In the December 1985 proposal, the agency disagreed with the Panel's recommendation as the product was manufactured only as a partially processed biological product and was intended for export and further manufacture (50 FR 51002 at 51007). The agency continues to agree with this approach inasmuch as the manufacturer continues to export the product as a partially processed biological. The product is not available as a finished product in the United States.

Category II. Licensed biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce. FDA does not propose that any products be placed in Category II.

Category IIIB. Biological products for which available data are insufficient to classify their safety and effectiveness and should not continue in interstate commerce. Table 2 of this document is a list of those products proposed by FDA for Category IIIB. We have not listed products for which FDA revoked the licenses before the December 1985 proposal but we identified them in the proposal. Products for which FDA revoked the licenses after the December 1985 proposal are identified in the "Comments" column.

FDA has revoked the licenses of all products proposed by FDA for Category IIIB. FDA proposes Category IIIB as the final category for the listed products.

TABLE 2.—CATEGORY IIIB

Manufacturer/License No.	Products	Comments
Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238	Diphtheria Toxoid	On July 27, 1993, FDA revoked the license for Diphtheria Toxoid at the request of the manufacturer
Connaught Laboratories, Inc., License No. 711	Diphtheria Toxoid, Pertussis Vaccine	On June 21, 1994, FDA revoked the license for Diphtheria Toxoid and on December 19, 1997, FDA revoked the license for Pertussis Vaccine, in both cases at the request of the manufacturer
Massachusetts Public Health Biologic Laboratories, License No. 64	Tetanus Toxoid	On October 11, 1989, FDA revoked the license for Tetanus Toxoid at the request of the manufacturer
Merck Sharpe & Dohme, Division of Merke & Co., Inc., License No. 2	Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Typhoid Vaccine	The manufacturer is now known as Merck & Co., Inc. On January 31, 1986, FDA revoked the licenses for all the listed products at the request of the manufacturer
Michigan Department of Public Health, License No. 99	Diphtheria Toxoid Adsorbed	On November 12, 1998, the name of the manufacturer was changed to BioPort, and the license number was changed to 1260. On November 20, 2000, FDA revoked the license for Diphtheria Toxoid Adsorbed at the request of the manufacturer
Wyeth Laboratories, Inc., License No.3	Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, Pertussis Vaccine	On May 19, 1987, FDA revoked the licenses for all listed products at the request of the manufacturer

IV. Anthrax Vaccine Adsorbed—Proposed Order

A. The Panel Recommendation that Anthrax Vaccine Adsorbed be Placed in Category I (Safe, Effective, and Not Misbranded)

In its report, the Panel found that Anthrax Vaccine Adsorbed (AVA), manufactured by Michigan Department of Public Health (MDPH, now BioPort) was safe and effective for its intended use and recommended that the vaccine be placed in Category I. In the December 1985 proposal, FDA agreed with the Panel's recommendation. During the comment period for the December 1985 proposal, FDA received no comments opposing the placement of AVA into Category I.

The Panel based its evaluation of the safety and efficacy of AVA on two studies: A well-controlled field study conducted in the 1950s, "the Brachman study" (Ref. 1a) and an open-label safety study conducted by the National Center for Disease Control (CDC, now the Centers for Disease Control and Prevention) (50 FR 51002 at 51058). The Panel also considered surveillance data on the occurrence of anthrax disease in the United States in at-risk industrial settings as supportive of the effectiveness of the vaccine (50 FR 51002 at 51059). In its proposed determination that the data support the safety and efficacy of AVA, FDA has identified points of disagreement with statements in the Panel report. However, FDA proposes that the data do support the safety and efficacy of the vaccine and, thus, FDA continues to accept the Panel's recommendation and proposes to place AVA in Category I.[4]

On October 12, 2001, a group of individuals filed a citizen petition requesting that FDA find AVA, as currently manufactured by BioPort, ineffective for its intended use, classify the product as Category II, and revoke the license for the vaccine. The petitioners complained that the December 1985 proposal that placed AVA in Category I had not been finalized. FDA responded separately in a written response to the petitioners on August 28, 2002 (Docket No. 2001P–0471), and FDA will not further address those issues in this proposal.

In March 2003, six plaintiffs, known as John and Jane Doe ı1 through ı6, filed suit in the United States District Court for the District of Columbia (the Court) seeking the Court to enjoin the Anthrax Vaccination Immunization Program (AVIP) of the Department of Defense (DoD), and to declare AVA an investigational drug when used for protection against inhalation anthrax. On December 22, 2003, the Court issued a preliminary injunction enjoining inoculations under the AVIP in the absence of informed consent or a Presidential waiver.

In the **Federal Register** of January 5, 2004 (69 FR 255), FDA published a final rule and final order amending the biologics regulations in response to the report and recommendations of the Panel. The final order placed AVA into Category I. Following FDA's issuance of the final rule and final order, the Court lifted the preliminary injunction on January 7, 2004, except as it applied to the six Doe plaintiffs.

On October 27, 2004, the Court issued a memorandum opinion vacating and remanding the January 2004 final rule and final order to FDA for reconsideration, following an appropriate notice and comment period. FDA is reopening the comment period on the entire Bacterial Vaccine and Toxoids efficacy review document for 90 days.

B. Efficacy of Anthrax Vaccine Adsorbed

The Brachman study included 1,249 workers in four textile mills in the northeastern United States that processed imported goat hair. Of these 1,249 workers, 379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations of

[4] In October 2000, the Institute of Medicine (IOM) convened the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. In March 2002, the Committee issued its report: The Anthrax Vaccine: Is It Safe? Does It Work? (Ref. 2). The report concluded that the vaccine is acceptably safe and effective in protecting humans against anthrax.

either vaccine or placebo, and 340 received no treatment but were monitored for the occurrence of anthrax disease as an observational group. The Brachman study used an earlier version of the protective antigen-based anthrax vaccine administered subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months. During the trial, 26 cases of anthrax were reported across the four mills: 5 inhalation and 21 cutaneous anthrax cases. Prior to vaccination, the yearly average number of human anthrax cases was 1.2 cases per 100 employees in these mills. Of the five inhalation anthrax cases (four of which were fatal), two received placebo and three were in the observational group. Of the 21 cutaneous anthrax cases, 15 received placebo, 3 were in the observational group, and 3 received anthrax vaccine. Of the three cases in the vaccine group, one case occurred just prior to administration of the third dose, one case occurred 13 months after the individual received the third of the six doses (but no subsequent doses), and one case occurred prior to receiving the fourth dose of vaccine.

In its report, the Panel stated that the Brachman study results demonstrate "a 93 percent (lower 95 percent confidence limit = 65 percent) protection against cutaneous anthrax" and that "inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease." (50 FR 51002 at 51058). On the latter point, FDA does not agree with the Panel report. Because the Brachman comparison of anthrax cases between the placebo and vaccine groups included both inhalation and cutaneous cases, FDA has determined that the calculated efficacy of the vaccine to prevent all types of anthrax disease combined was, in fact, 92.5 percent (lower 95 percent confidence interval = 65 percent). The efficacy analysis in the Brachman study includes all cases of anthrax disease regardless of the route of exposure or manifestation of disease. FDA agrees that the five cases of inhalation anthrax reported in the course of the Brachman study are too few to support an independent statistical analysis. However, of these cases, two occurred in the placebo group, three occurred in the observational group, and no cases occurred in the vaccine group. Therefore, we propose the indication section of the labeling for AVA not specify the route of exposure, and the vaccine be indicated for active immunization against *Bacillus anthracis*, independent of the route of exposure.[5]

As stated previously in this document, the Panel also considered epidemiological data—sometimes called surveillance data—on the occurrence of anthrax disease in at-risk industrial settings collected by the CDC and summarized for the years 1962-1974 as supportive of the effectiveness of AVA. In that time period, individuals received either vaccine produced by MDPH, now BioPort, or an earlier version of anthrax vaccine. Twenty-seven cases of anthrax disease were identified. Three cases were not mill employees but people who worked in or near mills; none of these cases had been vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with one dose, two with two doses); the remainder (89 percent) were unvaccinated (50 FR 51002 at 51058). These data provide confirmation that the risk of disease still existed for those persons who were not vaccinated and that those persons who had not received the full vaccination series (six doses) were susceptible to anthrax infection, while no cases occurred in those who had received the full vaccination series.

In 1998, the DoD initiated the Anthrax Vaccination Program, calling for mandatory vaccination of service members. Thereafter, concerns about the vaccine caused the U.S. Congress to direct DoD to support an independent examination of AVA by the IOM. The IOM committee reviewed all available data, both published and unpublished, heard from Federal agencies, the manufacturer, and researchers. The committee in its published report concluded that AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalation anthrax (Ref. 2). FDA agrees with the report's finding that certain studies in humans and animal models support the conclusion that AVA is effective against *B. anthracis* strains that are dependent upon the anthrax toxin as a mechanism of virulence, regardless of the route of exposure.[6]

C. Safety of Anthrax Vaccine Adsorbed

CDC conducted an open-label study under an investigational new drug application (IND) between 1967 and 1971 in which approximately 7,000 persons, including textile employees, laboratory workers, and other at-risk individuals, were vaccinated with anthrax vaccine and monitored for adverse reactions to vaccination. The vaccine was administered in 0.5-mL doses according to a 0-, 2-, and 4-week initial dose schedule followed by additional doses at 6, 12, and 18 months with annual boosters thereafter. Several lots, approximately 15,000 doses, of AVA manufactured by MDPH were used in this study period. In its report, the Panel found that the CDC data "suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare" (50 FR 51002 at 51059).

Subsequent to the publication of the Panel's recommendations, DoD conducted a small, randomized clinical study of the safety and immunogenicity of AVA. (See summary in product label. (Ref. 6)) These more recent DoD data as well as post licensure adverse event surveillance data available from the Vaccine Adverse Event Reporting System (VAERS) further support the safety of AVA (Ref. 7). These data are regularly reviewed by FDA, and provided the basis for a description of the types and severities of adverse events associated with administration of AVA included in labeling revisions approved by FDA in January 2002 (Ref. 6).

D. The Panel's General Statement: Anthrax Vaccine, Adsorbed, Description of Product

The Panel report states:

"Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonproteolytic, nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*" (50 FR 51002 at 51058).

FDA would like to clarify that while the *B. anthracis* strain used in the manufacture of BioPort's AVA is the nonproteolytic, nonencapsulated strain identified in the Panel report, it is not a mutant of the Vollum strain but was derived from a B. anthracis culture originally isolated from a case of bovine anthrax in Florida.

E. The Panel's Specific Product Review: Anthrax Vaccine Adsorbed: Efficacy

The Panel report states:

3. *Analysis—a. Efficacy—(2) Human.* The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman * * * in a placebo-controlled field trial in

[5] The Panel noted that it would be very difficult, if not impossible, to clinically study the efficacy of any anthrax vaccine (50 FR 51058). Further study raises ethical considerations, and the low incidence and sporadic occurrence of anthrax disease also makes further adequate and well-controlled clinical studies of effectiveness not possible.

[6] For example: The Brachman study (Ref. 1a); the CDC epidemiological data described in the December 1985 proposal; Fellows (2001) (Ref. 3); Ivins (1996) (Ref. 4); Ivins (1998) (Ref. 5).

mills processing imported goat hair * * *. The Michigan Department of Public Health vaccine is patterned after that of Merck Sharp & Dohme with various minor production changes.
(50 FR 51002 at 51059).

FDA has found that contrary to the Panel's statement, the vaccine used in the Brachman study was not manufactured by Merck Sharp & Dohme, but instead this initial version was provided to Dr. Brachman by Dr. G. Wright of Fort Detrick, U.S. Army, DoD (Ref. 1a). The DoD version of the anthrax vaccine used in the Brachman study was manufactured using an aerobic culture method (Ref. 8). Subsequent to the Brachman trial, DoD modified the vaccine's manufacturing process to, among other things, optimize production of a stable and immunogenic formulation of vaccine antigen and to increase the scale of manufacture. In the early 1960s, DoD entered into a contract with Merck Sharp & Dohme to standardize the manufacturing process for large-scale production of the anthrax vaccine and to produce anthrax vaccine using an anaerobic method. Thereafter, in the 1960s, DoD entered into a similar contract with MDPH to further standardize the manufacturing process and to scale up production for further clinical testing and immunization of persons at risk of exposure to anthrax spores. This DoD-MDPH contract resulted in the production of the anthrax vaccine that CDC used in the open-label safety study and that was licensed in 1970.

While the Panel attributes the manufacture of the vaccine used in the Brachman study to Merck Sharp & Dohme, FDA has reviewed the historical development of AVA and concluded that DoD's continuous involvement with, and intimate knowledge of, the formulation and manufacturing processes of all of these versions of the anthrax vaccine provide a foundation for a determination that the MDPH anthrax vaccine is comparable to the original DoD vaccine. See *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996). The comparability of the MDPH anthrax vaccine to the DoD vaccine has been verified through potency data that demonstrate the ability of all three versions of the vaccine to protect guinea pigs and rabbits against challenge with virulent *B. anthracis*. In addition, there are data comparing the safety and immunogenicity of the MDPH vaccine with the DoD vaccine. These data, while limited in the number of vaccines and samples evaluated, reveal that the serological responses to the MDPH vaccine and the DoD vaccine were similar with respect to peak antibody response and seroconversion.

F. The Panel's Specific Product Review: Anthrax Vaccine Adsorbed: Labeling

The Panel report states:

3. *Analysis*—d. *Labeling*: The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24 (a) (21 CFR 620.24(a)) defines a total primary immunizing dose as 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months).

(50 FR 51002 at 51059).

The dosing schedule for AVA has always consisted of six doses, a 0.5-mL dose at 0, 2, and 4 weeks, and then at 6, 12, and 18 months, followed by a subsequent 0.5-mL dose at 1 year intervals to maintain immunity. Prelicensure labels described the vaccination schedule as three initial doses, followed by three additional doses, and yearly subsequent doses, which is consistent with the additional standards of AVA that were originally published in October 1970, immediately before the licensure of AVA. The 1979 labeling referred to "primary immunization" as consisting of six injections, with recommended yearly subsequent injections. The 1987 labeling of AVA, subsequent to the Panel's report, described the vaccination schedule as "primary immunization" consisting of three doses followed by three additional doses for a total of six doses followed by annual injections. The labeling is not inconsistent with § 620.24(a) (21 CFR 620.24(a)) before it was revoked by FDA in 1996 as part of a final rule that revoked 21 CFR part 620 and other biologics regulations because they were obsolete or no longer necessary (Ref. 9). Thus while use of the term "primary" has varied over time in reference to the AVA vaccination schedule, the licensed schedule itself has always consisted of six doses of 0.5 mL administered at 0, 2, and 4 weeks and 6, 12, and 18 months, followed by additional doses on an annual basis to maintain immunity.

V. FDA's Responses to Additional Panel Recommendations

In the December 1985 proposal, FDA responded to the Panel's general recommendations regarding the products under review and to the procedures involved in their manufacture and regulation. Below, FDA responds again with its proposal to the general recommendations.

A. Generic Order and Wording of Labeling; Amendment of § 201.59

The Panel recommended changes to the labeling of the biological products under review. The Panel also recommended a generic order and wording for information in the labeling of bacterial vaccines. In the December 1985 proposal, FDA agreed with the labeling changes recommended by the Panel.

In the December 1985 proposal, FDA proposed that 6 months after publication of a final rule, manufacturers of products subject to this Panel review submit, for FDA's review and approval, draft labeling revised in conformance with the Panel's report and with the regulations. FDA proposed to require that the revised labeling accompany all products initially introduced or initially delivered for introduction into interstate commerce 30 months after the date of publication of the final rule. The proposed labeling review schedule was consistent with the scheduling provided in § 201.59 of the regulations.

Since the time of the Panel's recommendation, FDA has made a number of changes to the labeling regulations and related regulatory policies. FDA has added or revised the requirements in § 201.57 for including in the labeling, in standardized language, the information concerning use during pregnancy, pediatric use, and geriatric use. Section 201.57 requires a specific order and content for drug product labeling. A number of labeling sections included in § 201.57 were not included in the Panel's recommended ordering and wording of the labeling but are now required to help ensure clarity in the labeling. FDA has also provided guidance regarding the wording of sections in which the agency believes complete and consistent language is important. Because FDA regularly monitors labeling for the products subject to this Panel review to determine if the labeling is consistent with applicable labeling requirements, FDA does not believe that a labeling review is necessary at this time. Accordingly, FDA proposes to amend the table in § 201.59 by providing that the labeling requirements in §§ 201.56, 201.57, and 201.100(d)(3) (21 CFR 201.100(d)(3)) become effective on the date 30 months after the date of publication of the final rule. Because FDA regularly monitors the labeling of all products on an ad hoc basis, FDA also proposes to explain in a footnote to the table in § 201.59(a)(3) that specification of a date for submission of

revised product labeling under § 201.59 is unnecessary.

Section 314 of the National Childhood Vaccine Injury Act (NCVIA) of 1986 required FDA to review the warnings, use instructions, and precautionary information that are distributed with each vaccine listed in section 2114 of the Public Health Service Act and to determine whether this information was adequate to warn health care providers of the nature and extent of the dangers posed by such vaccine. Since the December 1985 proposal, FDA has completed this review and labeling has been revised accordingly. FDA is also taking this opportunity to propose updating the table in § 201.59(a)(3) to include the current mail codes for the review of labeling for various biological products.

B. Periodic Review of Product Labeling

In its report, the Panel noted a number of labeling deficiencies. To improve the labeling, the Panel recommended that labeling be reviewed and revised as necessary at intervals of no more than every 2 years.

As discussed in the December 1985 proposal, FDA believes the current system of labeling review will adequately assure accurate labeling. Periodic review of labeling on a set schedule is unnecessary. Section 601.12(f) prescribes when revised labeling must be submitted, either as a supplement for FDA's review or, if changes are minor, in an annual report. In addition, the agency may request revision of labeling when indicated by current scientific knowledge. FDA believes that, by these mechanisms, product labeling is kept up to date, and proposes that a scheduled, routine review of labeling is unnecessary and burdensome for both the agency and manufacturers.

C. Improvement in the Reporting of Adverse Reactions

The Panel recommended that actions be taken to improve the reporting and documentation of adverse reactions to biological products. The Panel particularly noted the need to improve the surveillance systems to identify adverse reactions to pertussis vaccine.

Since publication of the Panel's report, the Vaccine Adverse Event Reporting System (VAERS) was created as an outgrowth of the National Childhood Vaccine Injury Act (NCVIA) and is administered by FDA and Centers for Disease Control and Prevention (CDC). VAERS accepts from health care providers, manufacturers, and the public, reports of adverse events that may be associated with U.S.-licensed vaccines. Health care providers must report certain adverse events included in a Reportable Events Table (Ref. 10) and any event listed in the vaccine's package insert as a contraindication to subsequent doses of the vaccine. Health care providers also may report other clinically significant adverse events. FDA and CDC receive an average of 800 to 1,000 reports each month under the VAERS program. A guidance document is available which explains how to complete the VAERS form (Ref. 11).

D. Periodic Review of Product Licenses

The Panel recommended that all licensed vaccines be periodically reviewed to assure that data concerning the safety and effectiveness of these products are kept current and that licenses be revoked for products which have not been marketed for years or which have never been marketed in the licensed form. The Panel noted that, by limiting the period for which specific vaccines may be licensed, older products would be assured periodic review, and new products for which additional efficacy data are required could be provisionally licensed for a limited time period during which additional data can be generated.

In its proposed response, FDA noted that licensing policies in effect at the time of the review resulted in licenses being held for some products which were never intended to be marketed as individual products or which were no longer being marketed as individual products. FDA had required that manufacturers licensed for a combination vaccine also hold a license for each individual vaccine contained in the combination. For example, a manufacturer of diphtheria, tetanus, and pertussis (DTP) vaccine would also be required to have a license for Diphtheria Toxoid, Tetanus Toxoid, and Pertussis Vaccines. Because this policy is no longer in effect, most licenses are for currently marketed products. In a few cases, there may be no current demand for a product but, for public health reasons, a license continues to be held for the product. There are some vaccines for which there is little current demand but continued licensure could expedite the manufacture and availability of the product in the event an outbreak of the targeted disease should occur. FDA believes that the routine inspection of licensed facilities adequately assures that the information held in product licenses is current and that a routine review of safety and efficacy data is unnecessary and burdensome. The Panel's recommendation that some new vaccines be provisionally licensed for only limited periods of time while additional data are generated is inconsistent with the law that requires a determination that a biologic product is safe, pure, and potent before it is licensed.

E. Compensation for Individuals Suffering Injury From Vaccination

The Panel recommended that compensation from public funds be provided to individuals suffering injury from vaccinations that were recommended by competent authorities, carried out with approved vaccines, and where the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccines.

A compensation program has been implemented consistent with the Panel's recommendation. The NCVIA established the National Vaccine Injury Compensation Program (NVICP) designed to compensate individuals, or families of individuals, who have been injured by childhood vaccines, whether administered in the private or public sector. The NVICP, administered by the Health Resources and Services Administration, Department of Health and Human Services (HHS), is a no-fault alternative to the tort system for resolving claims resulting from adverse reactions to routinely recommended childhood vaccines. The specific vaccines and injuries covered by NVICP are identified in a Vaccine Injury Table that may periodically be revised as new vaccines come into use or new types of potential injuries are identified. The NVICP has resulted in a reduction in the amount of litigation related to injury from childhood vaccines while assuring adequate liability coverage and protection. The NVICP applies only to vaccines routinely recommended for infants and children. Vaccines recommended for adults are not covered unless they are routinely recommended for children as well, e.g., Hepatitis B Vaccine.

F. Public Support for Immunization Programs

The Panel recommended that both FDA and the public support widespread immunization programs for tetanus, diphtheria, and pertussis.

The National Immunization Program is part of CDC and was established to provide leadership to health agencies in planning and implementing immunization programs, to identify unvaccinated populations in the United States, to assess vaccination levels in state and local areas, and to generally promote immunization programs for children, including vaccination against diphtheria, tetanus, and pertussis. A

recent survey shows that nearly 95 percent of children 19 to 35 months of age have received three or more doses of any vaccine that contained diphtheria and tetanus toxoids (i.e., diphtheria and tetanus toxoids and pertussis vaccines (DTP), diphtheria and tetanus toxoids and acellular pertussis vaccines (DTaP) or diphtheria and tetanus toxoids vaccines (DT)) (Ref. 12).

G. Assuring Adequate Supplies of Bacterial Vaccines and Toxoids; Establishment of a National Vaccine Commission

The Panel recommended that FDA work closely with CDC and other groups to assure that adequate supplies of vaccines and passive immunization products continue to be available. The Panel recommended establishment of a national vaccine commission to address such issues.

Since the publication of the December 1985 proposal, the National Vaccine Program was created by Congress (Public Law 99–660) with the National Vaccine Program Office (NVPO) within HHS designated to provide leadership and coordination among Federal agencies as they work together to carry out the goals of the National Vaccine Plan. The National Vaccine Plan provides a framework, including goals, objectives, and strategies, for pursuing the prevention of infectious diseases through immunizations. The National Vaccine Program brings together all of the groups that have key roles in immunizations, and coordinates the vaccine-related activities, including addressing adequate production and supply issues. Despite efforts to assure vaccine availability, shortages may occur (Ref. 13) for a variety of reasons. FDA proposes to continue to work with the NVPO, the National Institutes of Health, CDC, and vaccine manufacturers to help facilitate continued vaccine availability making the establishment of a national vaccine commission unnecessary.

H. Consistency of Efficacy Protocols

The Panel recommended that the protocols for efficacy studies be reasonably consistent throughout the industry for any generic product. To achieve this goal, the Panel recommended the development of industry guidelines that provide standardized methodology for adducing required information.

FDA believes that the standardization of clinical testing methodology for a group of vaccines is often not practical or useful. Because of the variety of possible vaccine types, e.g., live vaccines, killed vaccines, toxoids, bioengineered vaccines, acellular vaccines, and the diversity of populations in which the vaccine may be studied, it is difficult to develop guidance that would apply to more than one or two studies. FDA routinely meets with manufacturers before the initiation of clinical studies to discuss the study and will comment on proposed protocols for efficacy studies. FDA proposes to continue to allow flexibility in selecting appropriate tests, procedures, and study populations for a clinical study while assuring that the necessary data are generated to fulfill the intended objectives of the study.

I. The Effect of Regulations Protecting and Informing Human Study Subjects on the Ability to Conduct Clinical Trials

The Panel expressed concern that the regulations governing informed consent and the protection of human subjects involved in clinical investigations should not establish unnecessary impediments to the goal of obtaining adequate evidence for the safety and effectiveness of a product.

FDA believes that the regulations and policies applying to informed consent and the protection of human subjects do not inhibit the adequate clinical study of a product. FDA notes that whenever the regulations or guidance documents related to these subjects are modified or amended, FDA offers an opportunity for public comment on the revisions. FDA particularly welcomes comments on how appropriate informed consent and protection of human subjects can be maintained while assuring that the development and study of useful products is not inhibited.

J. Standards for Determining the Purity of Diphtheria and Tetanus Toxoids (DTs)

The Panel recommended that standards should be established for purity of both DTs in terms of limits of flocculation (Lf) content per milligram (mg) of nitrogen.

In the December 1985 proposal, FDA agreed that standards should be set. FDA has since determined that this approach is overly restrictive; does not allow FDA to keep pace with advances in manufacturing and technology; and, proposes that standards for determining the purity of DTs not be established. The Center for Biologics Evaluation and Research (CBER) establishes the release specifications for the purity of DTs during the review of a Biologics License Application (BLA). The purity of diphtheria toxoids in currently licensed vaccines is usually at least 1,500 Lf/mg nondialyzable nitrogen. While there are no general standards for tetanus toxoid purity in the United States, CBER has generally required a purity specification of at least 1,000 Lf/mg of nondialyzable nitrogen for tetanus toxoids.

K. Immunogenic Superiority of Adsorbed Toxoids Over Fluid Toxoids

The Panel recommended that the immunogenic superiority of the adsorbed DTs over the fluid (plain) preparations be strongly emphasized in product labeling, especially with regard to the duration of protection.

Tetanus Toxoid fluid, manufactured by Aventis Pasteur, Inc., is the only fluid toxoid product that remains licensed in the United States in 2004. This product is licensed for booster use only in persons over 7 years of age. The current package insert for this product states that, although the rates of seroconversion are essentially equivalent with either type of tetanus toxoid, the adsorbed toxoids induce more persistent antitoxin titers than fluid products.

L. Laboratory Testing Systems for Determining Potency of Tetanus and Diphtheria Toxoids

The Panel noted a need for further studies with tetanus toxoids in a World Health Organization (WHO) sponsored quantitative potency test in animals to establish the conditions under which the test results are reproducible, and to relate these results more closely to those obtained in the immunization of humans. The Panel also recommended the development of an animal or laboratory testing system for diphtheria toxoid that correlates consistently, and with acceptable precision, with primary immunogenicity in humans.

DT-containing vaccines are tested during the licensing process for their ability to induce acceptable levels of protective antibodies in clinical trials in the target populations. Properties of vaccines used in these clinical trials, including potency, also are determined during licensing. The acceptance criteria for commercial lots of these vaccines are set at licensing on the basis of the properties of the vaccines that induced acceptable quantitative/qualitative levels of antibodies. The establishment of a correlation between a specific antibody response and a given assay would require an efficacy trial designed specifically to establish this correlation. This may call for vaccination of humans with sub-optimal doses of vaccine. Such an efficacy study is not feasible for ethical reasons.

The animal potency tests currently required by the WHO, the European Pharmacopoeia (EP), and FDA differ. Despite these differences, the potency

tests have been adequate to ensure sufficient immunogenic activity of the vaccines to induce protective immunity in target populations. However, international efforts to harmonize the diphtheria and tetanus potency tests under development are based on immunogenicity in animals. CBER is currently participating in these international harmonization efforts.

M. Potency Testing of DTs for Pediatric Use

The Panel recommended that the agency require potency testing after combination of the individual toxoid components in DTs for pediatric use.

FDA agrees with the recommendation. All manufacturers and the FDA testing laboratory follow this procedure on products submitted to the agency for release.

N. Potency Requirements for Pertussis Vaccine

The Panel recommended that the regulations concerning the maximum pertussis vaccine dose should be updated to reflect current recommendations and practices. At the time of the Panel review, whole cell pertussis vaccines were in use. Specifically, the Panel recommended that pertussis vaccine have a potency of four protective units per single human dose with the upper estimate of a single human dose not to exceed eight protective units. The Panel also recommended that the total immunizing dose be defined as four doses of four units each, compared to the three doses of four units each defined at the time of the recommendation in the regulations.

FDA has removed the additional standard regulations applicable to pertussis vaccine (Ref. 9). As whole cell pertussis vaccines are no longer licensed for human use in the United States, this recommendation no longer applies to products available in the United States.

O. Weight-Gain Test in Mice for Pertussis Vaccine

The Panel recommended that the weight-gain test in mice used to determine toxicity of pertussis vaccines be revised to include a reference standard and specifications regarding mouse strains to be used.

At the time of the Panel's deliberations, only DTP vaccines containing a whole-cell pertussis component were licensed in the United States. The mouse weight-gain test was a toxicity test used for whole-cell pertussis vaccines. Whole-cell pertussis vaccines are no longer licensed in the United States for human use, thus the mouse weight-gain test is no longer in use. Currently, only DTP vaccines containing an acellular pertussis component (DTaP) are licensed in the United States. These vaccines are tested specifically for residual pertussis toxin activity.

Although not currently licensed in the United States, vaccines containing a whole-cell pertussis component are still in use in other countries. CBER continues to participate in international efforts to improve the tests used to assess toxicity of whole-cell pertussis vaccines, including the mouse weight-gain test. CBER is represented on WHO committees and working groups with the goal of improving regulation and testing of whole-cell pertussis vaccines.

P. Agglutination Test to Determine Pertussis Vaccine Response in Humans

The Panel recommended that the agglutination test used to determine pertussis vaccine response in humans be standardized and that a reference serum be used for comparison. It also recommended that a reference laboratory be available at FDA.

As stated previously in this document, at the time of the Panel's deliberations, only whole-cell pertussis vaccines were licensed in the United States. The agglutination test was used for the clinical evaluation of DTP vaccines. Under the Panel's recommendations, FDA (CBER) developed and distributed reference materials for the agglutination assay and served as a reference laboratory. Currently, only DTaP vaccines are licensed in the United States. For the clinical evaluation of DTaP vaccines, the agglutination test was replaced by antigen-specific immunoassays, specifically enzyme-linked immunosorbent assays (ELISAs). As had been done with the agglutination assay, CBER took an active role in standardization of the ELISAs used to measure the specific antibody to the pertussis components of DTaP vaccines. Specifically, CBER distributes reference and control materials for the antigen-specific pertussis ELISA and has served as a reference laboratory.

Q. Warnings in Labeling for Pertussis Vaccine

The Panel recommended that the pertussis vaccine label warn that if shock, encephalopathic symptoms, convulsions, or thrombocytopenia follow a vaccine injection, no additional injections with pertussis vaccine should be given. The Panel also recommended that the label include a cautionary statement about fever, excessive screaming, and somnolence.

FDA agrees with the recommendation except that such information should be included in product labeling, i.e., the package insert, rather than the product label. Labeling applicable to the whole-cell pertussis vaccine conformed to this recommendation. Because the acellular form of pertussis vaccine has a different profile of potential adverse events and contraindications, the product labeling is worded consistent with available data.

R. Field Testing of Fractionated Pertussis Vaccines

The Panel recommended that any fractionated pertussis vaccine that differs from the original whole cell vaccine be field tested until better laboratory methods for evaluating immunogenicity are developed. The Panel recommended that the field-testing include agglutination testing and, if possible, evaluation of clinical effectiveness.

The currently approved vaccines containing an acellular pertussis component were studied in the United States and abroad in human populations with the antibody response being measured and clinical effectiveness evaluated.

S. Use of Same Seed Lot Strain in Manufacturing Bacillus Calmette-Guerin (BCG) Vaccine

The Panel recommended that all BCG vaccines be prepared from the same seed lot strain with demonstrated efficacy, if available data justify such action.

BCG vaccines are not recommended for routine immunization in the United States. The two currently U.S.-licensed BCG vaccines are produced using different seed strains. Most BCG vaccines produced globally are manufactured using seed strains with a unique history. Recent evidence suggests that these different BCG strains do differ genetically and have slightly varying phenotypes. However, a meta analysis of the current human BCG vaccination data performed in 1994 by Harvard University concluded that no strain-to-strain differences in protection could be detected. Although there have been differences in immunogencity among strains demonstrated in animal models, no significant differences have been seen in human clinical trials (Ref. 14). Thus, FDA does not find that available human data justify requirement of a single BCG vaccine strain.

T. Development of an Improved Cholera Vaccine

The Panel recommended public support for development of an improved cholera vaccine because unsatisfactory sanitary conditions in many countries make it clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

Cholera is not an endemic disease in the United States. However, there is risk to U.S. travelers to certain countries where the disease is endemic. FDA continues to cooperate with international health agencies in efforts to evaluate new types of vaccines and to study the pathogenesis of the disease. CBER personnel have chaired and participated in the WHO Cholera Vaccine Standardization Committee and have participated in drafting new WHO guidelines for immune measurement of protection from cholera.

U. Plague Vaccine Immunization Schedule

The Panel recommended that the following plague vaccine immunization schedule be considered:

1. A primary series of 3 intramuscular (IM) injections (1 mL, 0.2 mL, and 0.2 mL), 1 and 6 months apart, respectively;
2. Booster IM injections of 0.2 mL at 12, 18, and 24 months; and,
3. For persons achieving a titer of 1:128 after the third and fifth inoculations, booster doses when the passive agglutination titer falls below 1:32 and empirically every 2 years when the patient cannot be tested serologically.

FDA agrees with the recommendation, and the currently licensed vaccine is labeled consistent with the recommendation.

VI. FDA's Response to General Research Recommendations

In its report, the Panel identified many areas in which there should be further investigation to improve existing products, develop new products, develop new testing methodologies, and monitor the population for its immune status against bacterial disease. In the December 1985 proposal, FDA responded to these recommendations in the responses identified as items 11, 17 (in part), 21, 25, and 27. As discussed in the December 1985 proposal, FDA considered the Panel's recommendations in defining its research priorities at the time the recommendations were made. Because a considerable amount of time has elapsed since these recommendations were made and FDA initially responded to the recommendations, FDA is not providing specific responses to each recommendation. As in any area of scientific research, new discoveries and new concerns require a continual reevaluation of research priorities and objectives to assure their relevance to current concerns.

FDA recognizes the Panel's desire to have FDA's research program evolve with the significant issues and findings of medical science. In order to assure the continued relevance of its research program, CBER's research program for vaccines, including bacterial vaccines and related biological products, is subject to peer review by the Panel's successor, the Vaccines and Related Biological Products Advisory Committee (see, for example, the transcripts from the meetings of June 11 (Ref. 15) and November 29, 2001 (Refs. 16 and 17), and March 6, 2002 (Ref. 18)). In addition, CBER has defined as part of its mission statement a strategic goal of assuring a high quality research program that contributes directly to its regulatory mission. This goal includes a plan to assure that CBER's research program continues to support the regulatory review of products and timely development of regulatory policy, and to have a significant impact on the evaluation of biological products for safety and efficacy.

Because of limited resources, FDA also supports the leveraging of resources to create effective collaborations in the advancement of science. FDA has issued a "Guidance for FDA Staff: The Leveraging Handbook, an Agency Resource for Effective Collaborations." (Ref. 19). Through cooperation with international, other Federal, and State health care agencies and the industry and academia, the agency intends that its research resources will reap the benefits of a wide range of experience, expertise, and energy from the greater scientific community while the agency maintains its legal and regulatory obligations. FDA invites comment at any time on ways it may improve its research program and set its objectives.

VII. Proposed Amendment to the Regulations

In the December 1985 proposal, FDA proposed to amend § 610.21 (21 CFR 610.21), limits of potency, by revising the potency requirements for Tetanus Immune Globulin (Human) (TIG). FDA proposed to amend the regulations to require a minimum potency of 250 units of tetanus antitoxin per container for TIG. FDA advises that in this discussion and in the proposed regulation, "per container" means that amount of the contents of the container deliverable to the patient in normal use. The current regulation provides for a minimum potency of 50 units of tetanus antitoxin per milliliter of fluid. FDA proposes the change because the concentration of antitoxin per milliliter has varied widely in the past without any apparent effect on the performance of the product. TIG is routinely manufactured consistently at a concentration of 170 units per milliliter. However, there was no evidence upon which to establish a revised minimum potency on a per milliliter basis. Because the evidence of efficacy for TIG was based on use of product administered consistently at doses of 250 units or larger and the varying concentration of the product without any apparent adverse effect, FDA proposes that it is more appropriate to regulate the potency on a per vial basis, rather than by units per milliliter. The current licensed product continues to be marketed at a potency no less than the minimum dose (250 units), which historically has been shown to be clinically effective.

FDA received no comments opposing the proposed revision to § 610.21 and therefore proposes to amend the regulations to require a minimum potency of 250 units of tetanus antitoxin per container for TIG.

VIII. Analysis of Impacts

A. Review Under Executive Order 12866, the Regulatory Flexibility Act, and the Unfunded Mandates Act of 1995

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant economic impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact on small entities. The Unfunded Mandates Reform Act requires that agencies prepare a written statement under section 202(a) of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, or tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation) in any one year.

The agency believes that this proposed rule is consistent with the

regulatory philosophy and principles identified in the Executive Order. In addition, this proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order. Because this proposed rule does not impose new requirements on any entity it has no associated compliance costs, and the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required. Because this proposed rule does not impose mandates on State, local, or tribal governments, in the aggregate, or the private sector, that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost benefit analysis under the Unfunded Mandates Reform Act. The current inflation adjusted statutory threshold is approximately $110 million.

B. Environmental Impact

The agency has determined, under 21 CFR 25.31(h), that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

C. Paperwork Reduction Act of 1995

This proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

D. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

X. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm.1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. The full Panel Report was incorporated into the "Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review," proposed rule, published in the **Federal Register** of December 13, 1985 (50 FR 51002).

1a. Brachman, P. S.; H. Gold; S. Plotkin; F. R. Fekety; M. Werrin; and N. R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," *American Journal of Public Health*, 52:632–645, 1962.

2. Joellenbeck, Lois M.; Lee L. Zwanziger; Zane S. Durch; and Brian L. Strom; Editors, Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, Medical Follow-Up Agency, The National Academies Press, Washington, DC, April 2002, *http://www.nap.edu/catalog/10310.html* (FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**).

3. Fellows, P. F.; M. K. Linscott; B. E. Ivins; M. L. M. Pitt; C. A. Rossi; P. H. Gibbs and A. M. Friedlander, "Efficacy of a Human Anthrax Vaccine in Guinea Pigs, Rabbits, and Rhesus Macaques Against Challenge by Bacillus Anthracis Isolates of Diverse Geographical Origin," *Vaccine* 19(23/24):3241–3247, 2001.

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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated by the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 201 and 610 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C 216, 241, 262, 264.

2. Section 201.59 is amended in the table in paragraph (a)(3) by:

a. Removing "HFB–240" everywhere it appears and adding in its place "HFM–99" in the BIOLOGICS section of the table, under "Mail Routing Code";

b. Revising the entries for the drug classes "Bacterial vaccines and toxoids with standards of potency" and "Viral and rickettsial vaccines" in the BIOLOGICS section of the table to read as follows.

§ 201.59 Effective date of §§ 201.56, 201.57, 201.100(d)(3), and 201.100(e).

(a) * * *

(3) * * *

Effective	Revised labeling due	Drug class	Mail routing code
	Biologics		
[Insert date 30 months after date of publication in the **Federal Register**]	See footnote[3]	Bacterial vaccines and toxoids with standards of potency	HFM–99
* * *	* * *	* * *	*
Nov. 1, 1982[1]	Nov 1, 1980[2]	Viral and rickettsial vaccines	HFM–99
* * *	* * *	* * *	*

[1] Except the effective date for all biological products reviewed generically by the advisory panel is 30 months after a final order is published under § 601.25(g) of this chapter.

[2] Except the due date for all biological products reviewed generically by the advisory panel is 6 months after a final order is published under § 601.25(g) of this chapter.

[3] FDA has determined that a review of product labeling under this section is unnecessary.

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PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

3. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

4. Section 610.21 is amended by revising the entry "Tetanus Immune Globulin (Human), 50 units of tetanus antitoxin per milliliter" under the heading "ANTIBODIES" to read as follows:

§ 610.21 Limits of potency.

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ANTIBODIES

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Tetanus Immune Globulin (Human), 250 units of tetanus antitoxin per container.

* * * * *

Dated: December 21, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–28322 Filed 12–23–04; 11:16 am]

BILLING CODE 4160–01–S